

## PATENT COOPERATION TREATY

## PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT  
(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference JBV/P33071	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP 03/06754	International filing date (day/month/year) 25.06.2003	Priority date (day/month/year) 26.06.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/535		
Applicant GLAXO GROUP LIMITED et al.		

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 10 sheets, including this cover sheet.  
  
☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).  
  
 These annexes consist of a total of    sheets.

## 3. This report contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand  03.12.2003	Date of completion of this report  12.08.2004
Name and mailing address of the International preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer  Stroeter, T  Telephone No. +49 89 2399-8088  

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP 03/06754

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, Pages**

1-64 as originally filed

**Claims, Numbers**

1-16 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
  - ☐ the language of publication of the international application (under Rule 48.3(b)).
  - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:
- ☐ contained in the international application in written form.
  - ☐ filed together with the international application in computer readable form.
  - ☐ furnished subsequently to this Authority in written form.
  - ☐ furnished subsequently to this Authority in computer readable form.
  - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
  - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

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**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 10

because:

☒ the said international application, or the said claims Nos. 10 relate to the following subject matter which does not require an international preliminary examination (specify):

**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

**IV. Lack of unity of invention**

1. In response to the invitation to restrict or pay additional fees, the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☒ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

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☐ all parts.

☒ the parts relating to claims Nos. 1-8, 10-16 (each partial), 9 (complete) .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;  
citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes: Claims	2, 8, 9
	No: Claims	1, 3-7, 10-16
Inventive step (IS)	Yes: Claims	2, 8, 9
	No: Claims	1, 3-8, 10-16
Industrial applicability (IA)	Yes: Claims	1-9, 11-16
	No: Claims	

**2. Citations and explanations**

**see separate sheet**

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EXAMINATION REPORT - SEPARATE SHEET**

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**Re Item I**

**Basis of the opinion**

As set out in item IV, the present application lacks unity and is divided into five groups of inventions. Since the Applicant had only inventions 1 and 3 searched and furthermore paid the examination fees for these inventions, the following opinion is given on those parts relating to these inventions 1 and 3.

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claim 10 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**Re Item IV**

**Lack of unity of invention**

The application as filed is considered to lack unity of invention since its subject-matter relates not to one but rather to 5 separate inventions as follows:

1. Claims: 1, 3-8, 10-16 (each partial)

compounds (and subject-matter referring to these compounds) of formula (I) wherein  $R^A$  is a carbocyclic bicyclic system.

2. Claims: 1-6, 10-16 (each partial)

compounds (and subject-matter referring to these compounds) of formula (I) wherein  $R^A$  is a heterocyclic bicyclic system and  $R^B$  is a carbocyclic bicyclic system.

3. Claims: 1-8, 10-16 (each partial); 9 (complete)

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compounds (and subject-matter referring to these compounds) of formula (I) wherein  $R^A$  is a heterocyclic bicyclic system and  $R^5$  is a heterocyclic bicyclic system wherein ring (a) is aromatic and ring (b) is non-aromatic.

4. Claims: 1-7, 10-16 (each partial)

compounds (and subject-matter referring to these compounds) of formula (I) wherein  $R^A$  is a heterocyclic bicyclic system and  $R^5$  is a heterocyclic bicyclic system wherein ring (a) is non-aromatic and ring (b) is aromatic.

5. Claims: 1-7, 10-16 (each partial)

compounds (and subject-matter referring to these compounds) of formula (I) wherein  $R^A$  is a heterocyclic bicyclic system and  $R^5$  is a heterocyclic bicyclic system wherein both rings (a) and (b) are aromatic.

These groups presented in the order chosen by the Applicant are not so linked as to form a single general inventive concept as required by Rules 13.1 and 13.2 PCT for the following reasons: The identified 5 inventions involve as common structural principle that a bicyclus (here:  $R^A$ ) is linked to a piperidine ring which itself is linked to another bicyclus (here:  $R^5$ ). Structures of such a type are already known from prior art document WO0208224 (D1) wherein various compounds are described possessing two bicyclic rings which are similarly linked and which also possess antibacterial activity. Thus the technical problem underlying the present application is seen in the provision of further antibacterial compounds and the contributions claimed in the present applications which are possibly made over the prior art are:

(1) the provision of further antibacterials by replacing the bicyclic heterocyclic substituents disclosed in the compounds of D1 corresponding to present  $R^A$  with bicyclic carbocycles.

(2) the provision of further antibacterials by replacing the bicyclic heterocyclic substituents disclosed in the compounds of D1 corresponding to present  $R^5$  with bicyclic carbocycles.

(3) the provision of further antibacterials by replacing the bicyclic heterocyclic substituents disclosed in the compounds of D1 corresponding to present  $R^5$  with

bicyclic heterocycles wherein only ring (a) is aromatic.

(4) the provision of further antibacterials by replacing the bicyclic heterocyclic substituents disclosed in the compounds of D1 corresponding to present R<sup>5</sup> with other bicyclic heterocycles wherein only ring (b) is aromatic.

(5) the provision of further antibacterials by replacing the bicyclic heterocyclic substituents disclosed in the compounds of D1 corresponding to present R<sup>5</sup> with other bicyclic heterocycles wherein both rings (a) and (b) are aromatic.

**Remark: Since heterocyclic bicyclic substituents corresponding to R<sup>5</sup> or "ring A", respectively, are known from D1 wherein either only ring (b) or both rings (a) and (b) are aromatic, groups 4 and 5 contains various compounds which have no common link among themselves.**

These contributions, however, have nothing more in common than each single of these contributions has in common with the mentioned prior art. In other words, starting from D1 these contributions diverge in at least five different directions and are, thus, not so linked as to form one single inventive concept which would support unity of the invention.

**Re Item V**

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Only subject-matter of groups 1 and 3 was considered in the International Preliminary Examination as explained under item I.

**1 Prior art documents**

Reference is made to the following documents. The given numbering will be adhered to in the rest of the procedure:

D1: WO 02/08224 A (DAVIES DAVID THOMAS ;MARKWELL ROGER  
EDWARD (GB); JONES GRAHAM ELGI) 31 January 2002

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- D2: WO 02/056882 A (DAVIES DAVID THOMAS ;MARKWELL ROGER EDWARD (GB); JONES GRAHAM ELGI) 25 July 2002  
D3: WO 03/064421 A (GLAXO GROUP LTD ;PEARSON NEIL DAVID (GB); SEEFELD MARK ANDREW (US)) 7 August 2003  
D4: WO 03/064431 A (GLAXO GROUP LTD ;PEARSON NEIL DAVID (GB); SEEFELD MARK ANDREW (US)) 7 August 2003  
D5: US-B-6 323 2172 (POITEVIN CHRISTOPHE ET AL) 27 November 2001  
D6: EP-A-0 445 862 (JANSSEN PHARMACEUTICA NV) 11 September 1991  
D7: GB-A-1 375 836 (JOHN WYETH & BROTHER LTD.) 27 November 1974  
D8: US-A-5 610 157 (VAN DAELE GEORGES H P ET AL) 11 March 1997

P-document D2 and E-documents D3 and D4 do not form part of the state of the art according to Rule 64.1(b) PCT and are not further considered in the international preliminary examination. For the purposes of this communication the priorities of the present application and the above prior art have not been checked and it has been assumed that they are valid.

D1-D4 are related to compounds having a similar activity than the present ones, i.e. being antibacterials. D5-D8 are related to subject-matter of different technical fields.

**2 Novelty (Article 33(2) PCT) and inventive step (Article 33(3) PCT)**

The present application is directed to antibacterial compounds comprising a bicyclus ( $R^A$ ) that is linked to a piperidine ring which itself is linked to another bicyclus ( $R^5$ ).

D1 claims and exemplifies compounds wherein a bicyclic heterocycle (corresponding to present  $R^A$ ) is linked to a bicyclic carbocyclic or heterocyclic system (corresponding to  $R^5$ ) wherein ring (b) is always aromatic and ring (a) can be aromatic or non-aromatic (see examples).

D5 claims and exemplifies compounds wherein a inden or benzofurane moiety (corresponding to present  $R^A$ ) is linked to i.a. bicyclic heterocycles (corresponding to present  $R^5$ ) like 1,2,3,4-tetrahydroisoquinolin(5-yl), i.e. wherein ring (a) is aromatic and ring (b) is non-aromatic (see examples).

D6, D7 and D8 claim and exemplify compounds wherein bicyclic heterocycles (corresponding to present  $R^A$ ) like indole are linked to bicyclic heterocycles



(corresponding to present  $R^5$ ) wherein ring (a) is aromatic and ring (b) is non-aromatic (see e.g. example 9, co.nr. 45 of D6 and example 13 of D7).

- 2.1 First group: Claims 1, 3-8, 10-16 (each partial) comprising compounds wherein a carbocyclic bicyclic system ( $R^A$ ) is linked to a bicyclic carbocyclic or heterocyclic system ( $R^5$ ).

A part of the compounds of the first group claimed in present claims 1 and 3-7 is anticipated by the content of the document D5, examples 5, 21, 23, 41, 44, 86 and claims therein. Consequently, present claims 10-16 are not novel, too. No bicyclic carbocycles corresponding to present  $R^A$  are claimed and/or exemplified in D1 and D6 to D8 which are thus not relevant for the question of novelty.

Those compounds of claim 8 are novel due to the specific  $R^5$  moieties mentioned.

In view of the closest prior art D1, the present problem is to be seen in the provision of further structurally related antibacterials.

Since no example compounds having a carbocyclic moiety  $R^A$  are present in the present application, there is no evidence that the abovementioned technical problem has been successfully solved and consequently the requirements for inventive step are not fulfilled for the subject-matter of group 1.

- 2.2 Third group: Claims 1-8, 10-16 (each partial) and 9 (complete) comprising compounds wherein  $R^A$  is a heterocyclic bicyclic system and  $R^5$  is a heterocyclic bicyclic system wherein ring (a) is aromatic and ring (b) is non-aromatic.

A part of the compounds of the third group claimed in present claims 1, 3-7 is anticipated by the content of the document D5, e.g. examples 73, 75 and the claims therein. Likewise, D6 to D8 are novelty-destroying, see e.g. example 9, co.nr. 45 of D6 and example 13 of D7 and claims therein. Consequently, present claims 10-16 are not novel, too, whereas claims 2, 8 and 9 are novel.

The compounds of D1 are not novelty-destroying since ring (b) in the bicycles corresponding to present  $R^5$  is always aromatic.

The abovementioned problem has been solved by modifying the compounds of D1, i.e. replacing the bicyclic heterocycle moiety  $R^5$  of D1 wherein the ring (b) is

always aromatic with a bicyclic heterocycle moiety  $R^5$  as in present formula (I) wherein ring (b) is always non-aromatic. There's no teaching in D1 or any other relevant prior art document that ring (b) could be non-aromatic and as such the novel subject-matter, i.e. at present subject-matter of claims 2, 8 and 9, implies an inventive step.

**3 Industrial applicability (Article 33(4) PCT)**

The subject-matter of the present claims 1 to 9 and 11-16 is in accordance with the requirements of Article 33(4) PCT.

For the assessment of the present claim 10 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**4 Further requirements of the PCT**

For the present application the ISA issued a search report wherein it was noted that claims 1-7 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed, i.e. a combination of claims 2, 5 and 8 with the definitions for  $R^A$ ,  $R^5$ , n, A and B given therein.